Please add the following new claim.

67. (New) A protein linked to an exogenous protein surface loop, wherein the exogenous protein surface loop consists of an optimized protein surface loop that specifically binds a selected target, and replaces an endogenous protein surface loop on the protein, and wherein the protein is selected from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand.

Please cancel claims 3 and 66 without prejudice.

REMARKS

Claims 3, 13-24, 65 and 66 are pending in the present application. Claims 13-24 and 65 are amended herein for clarity and to more particularly define the invention. Support for these amendments can be found in the language of claims 13-24 as originally filed, in claim 65 as originally filed, in the support for new claim 67 and throughout the specification. Claims 3 and 66 are canceled herein without prejudice. New claim 67 is added herein. Support for this new claim can be found on page 13, lines 4-21, page 14, lines 22-30, and page 15, lines 12-20, and throughout the specification. It is believed that no new matter has been added by these amendments or this new claim. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application, entry of these amendments and the new claim and allowance of the pending claims to issue.

Applicants wish to thank Examiner DiBrino for taking the time to participate in a telephone interview on August 15, 2001 with Dr. Jeffrey Smith, Dr. Edward Madison, Dr. Mary Miller and Dr. Lizette Fernandez to discuss the pending claims. During this telephone interview, new claim 67 and the outstanding rejections were discussed. The following remarks address the specific rejections under 35 U.S.C. § 112, first paragraph in the context of this discussion.

I. Rejections Under 35 U.S.C. § 112, first paragraph

A. The Office Action states that claims 3, 13-24, 65 and 66 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Office Action, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed: 1) protein consisting of a grafted optimized protein surface loop that specifically binds to a selected target, wherein the protein surface loop is not endogenous to the protein and replaces a surface loop on the protein; 2) wherein the target is a biological entity, a synthetic or naturally occurring macromolecule, a protein or an "IgG-like" molecule. The instant claims encompass a protein consisting of a protein surface loop that is not endogenous to said protein and replaces a surface loop on the protein (i.e., the protein consists of the protein surface loop), and wherein the target is a biological entity, including an organism or a human, a synthetic or naturally occurring macromolecule, including synthetic macromolecules not found

in nature or in a living organism, as well as any naturally occurring organic or inorganic macromolecule. The Office Action concludes that there is insufficient disclosure in the specification for such a protein and such targets.

New claim 67 recites a protein linked to an exogenous protein surface loop, wherein the exogenous protein surface loop consists of an optimized protein surface loop that specifically binds a selected target, and replaces an endogenous protein surface loop on the protein, and wherein the protein is selected from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand. New claim 67 does not describe a protein consisting of the protein surface loop or a peptide. Furthermore, applicants have adequately described the types of proteins that can be linked to an exogenous protein surface loop. For example, on page 13, lines 5-18 of the specification, numerous proteins are listed, such as a synthetic or naturally occurring enzyme (such as a protease, a phosphatase, a kinase, P450, or other drug metabolizing enzymes, superoxide dismutases or nitric oxide synthase); a thrombolytic agent (such as tissue plasminogen activator, uPA, vampire bat tPA, staphylokinase, streptokinase, an acylated streptokinase-plasminogen complex, or variants of any of the preceding); an anticoagulant (such as an inhibitor of the members of the blood coagulation cascade, antagonists of integrin adhesion receptors, protein C or activated protein C, tissue factor pathway inhibitor, or variants of blood coagulation enzymes like Factor VII, factor X or thrombin, inhibitors of platelet function, inhibitors of Factor XIII, compounds which modulate the activity of a protein involved in blood coagulation (for example, heparin), or any variant of the above); an apoptotic agent; a growth factor; a cytokine; and other

ligands for cell surface receptors. Therefore, applicants believe there is sufficient disclosure in the application for the types of proteins that can be linked to an exogenous surface loop that consists of an optimized protein surface loop that specifically binds a selected target, and replaces an endogenous protein surface loop on the protein, according to the teachings of the present invention.

With respect to targets bound by the proteins of the present invention, applicants agree with the Examiner's acknowledgment during the interview that a list of targets is disclosed in the specification on page 13, lines 23-31 and page 14, lines 1-6 of the specification. Thus, applicants believe there is sufficient disclosure in the specification of targets for binding of the protein of the claimed invention and respectfully request withdrawal of this rejection.

According to the Office Action, the specification discloses that a surface loop is defined as a binding, i.e., targeting element of a protein, which element is a flexible loop structure in the native protein of about 2 to about 20 amino acids that either connects regions of defined secondary structure in the native protein or connects a domain of secondary structure and a terminus of the native protein and which element is selective for binding to one or more binding sites. The specification further discloses a list of "targets." Targets include, but are not limited to, for example, any region, tissue, organ, cell, virus, organelle, microorganism, synthetic or naturally occurring molecule or macromolecule, a modified variant thereof, a protein, a receptor, a proteoglycan, an ion channel, a biological entity, or a component of a pathologic lesion. The specification also discloses, as an example, tPA protein, comprising an optimized surface loop

from Fab-9 mAb which binds β3-integrins. According to the Office Action, the instant disclosure does not adequately describe the scope of the claimed invention, which encompasses a substantial variety of subgenera. Specifically, the Office Action states that, since the disclosure fails to provide sufficient relevant identifying characteristic that identify members of the genus, and given the broad genus claimed, the disclosure of the tPA/Fab-9 surface loop protein is insufficient to describe the claimed genus. The Office Action alleges that there are insufficient identifying characteristics disclosed by the instant specification for the claimed proteins/targets.

As stated above, applicants have provided numerous examples of proteins that can be linked to an exogenous surface protein loop, as well as examples of targets for binding of the protein of new claim 67. Furthermore, a surface loop is defined in the specification as a binding, i.e., targeting element of a protein which element is a flexible loop structure in the native protein of about 2 to about 20 amino acids that either connects regions of defined secondary structure in the native protein or connects a domain of secondary structure and a terminus of the native protein and which element is selective for binding to one or more binding sites. In the protein of new claim 67, the surface loop must be an optimized surface loop, which is defined in the specification as a polyamino acid that has been manipulated to increase its natural affinity for its target binding site (see page 14, line 16-17).

Therefore, one of skill in the art would clearly know, from the teachings of the specification, how to identify a protein linked to an exogenous protein surface loop, wherein the exogenous protein surface loop consists of an optimized protein surface loop that specifically

binds a selected target, and replaces an endogenous protein surface loop on the protein, and wherein the protein is selected from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand. Also from these teachings, one of skill in the art could make any protein linked to an exogenous protein surface loop, wherein the exogenous protein surface loop consists of an optimized protein surface loop that specifically binds a selected target, and replaces an endogenous protein surface loop on the protein, and wherein the protein is selected from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand according to the teachings of the present invention and assay the resultant protein for specific binding to a target as described in the application and as known in the art.

Furthermore, it is clear from the teachings of the specification that, although the proteins and their targets of the present invention may vary in structure, all of the proteins of the claimed invention must have a core structure, i.e., a protein surface loop that consists of an optimized protein surface loop that specifically binds a selected target, and replaces an endogenous protein surface loop on the protein. This surface loop must be from about 2 to 20 amino acids in length and possess an increase in its natural affinity for its target binding site.

Applicants also point out that, according to page 1104 of the Written Description Guidelines set forth in the *Federal Register* on January 5, 2001, an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such

descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. On page 1106 of the Written Description Guidelines, it is stated that an applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.

Applicants believe the requirements set forth in the Written Description Guidelines have been met for the present invention and respectfully point out that the specification and claims do provide sufficient identifying characteristics shared by the members of the claimed genus. Both the specification and the claims place a limit on the kinds of proteins, i.e., an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand, that are considered members of the genus and provide limitations on the structure of the surface loop and its binding properties, i.e., a loop structure of about 2 to about 20 amino acids that has been manipulated to increase its natural affinity for its target binding site. In particular, one of skill in the art would clearly know what an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand are based on the examples of these proteins set forth in the specification and from what is well known in the art about these types of proteins. Enzymes, thrombolytic agents, anticoagulants, apoptotic proteins, growth factors, cytokines and cell surface receptor ligands have well-defined

functional properties that are accepted and recognized as identifying functional characteristics by those skilled in the art. This knowledge, coupled with the teachings of the specification would allow anyone to obtain the proteins of the claimed invention. Therefore, one of skill in the art would reasonably conclude that applicants were in possession of the necessary common attributes possessed by the members of the genus and thus have provided sufficient written description for the proteins of the present invention. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

B. The Office Actions states that claims 3, 13-24, 65 and 66 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. According to the Office Action, this is a new matter rejection. The amendatory material not supported by the specification and claims as originally filed is "wherein the protein is not an antibody."

Claim 3 is canceled herein without prejudice and claims 13-24, 65 and 66 are amended herein to no longer depend from claim 3, thus rendering this rejection moot and applicants respectfully request its withdrawal.

C. Claims 3, 13-24, 65 and 66 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the intention. Specifically, the Office Action states that the specification does not disclose how to make and/or use a protein consisting of a grafted protein surface'loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, and replaces a surface loop on the protein. According to the Office Action, the specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a protein that is a peptide. Further stated in the Office Action is that there is insufficient guidance in the specification as to how to make and/or use the instant invention and that there is no disclosure in the specification as to making/using a protein consisting of a grafted optimized protein surface loop. Therefore, the Office Action alleges that undue experimentation would be required of one skilled in the art to practice the instant invention.

As stated above, new claim 67 recites a protein linked to an exogenous protein surface loop, wherein the exogenous protein surface loop consists of an optimized protein surface loop that specifically binds a selected target, and replaces an endogenous protein surface loop on the protein, and wherein the protein is selected from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand. Therefore, new claim 67 does not describe a protein consisting of the protein surface loop. Furthermore, as noted above, it is clear that one of skill in the art can make any protein linked to an exogenous protein surface loop, wherein the exogenous protein surface loop consists of an optimized protein surface loop that specifically binds a selected target, and replaces an endogenous protein surface loop on the protein, and wherein the protein is selected

from the group consisting of an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine and a cell surface receptor ligand according to the teachings of the present invention and assay the resultant protein for specific binding to a target as described in the specification and as is well known in the art. Therefore, applicants believe sufficient guidance is provided in the specification as to how to make/and or use the claimed invention. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

II. Rejections Under 35 U.S.C. § 112, second paragraph

A. The Office Action states that claim 24 recites the limitation "targeted agent" in line 1. There is allegedly insufficient basis for this limitation in the claim because base claim 23 does not recite the said limitation.

Claim 24 is amended herein to no longer recite "targeted agent." Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

B. Further stated in the Office Action is that Claim 19 is allegedly indefinite in the recitation of "Arg-Gly-Asp (RGD) tripeptide motif" because it is ambiguous to recite a limitation in parentheses.

Claim 19 is amended herein to no longer recite a limitation in parentheses. Thus, applicants believe this rejection has been overcome and applicants respectfully request its withdrawal.

C. The Office Action states that claim 24 is allegedly indefinite in the recitation of "(CDR3)" because it is ambiguous to recite a limitation within parentheses.

Claim 24 is amended herein to no longer recite a limitation in parentheses. Thus, applicants believe this rejection has been overcome and applicants respectfully request its withdrawal.

D. The Office Action states that claim 65 is indefinite in the recitation of "(LG-tPA)" because it is ambiguous to recite a limitation within parentheses.

Claim 65 is amended herein to no longer recite a limitation in parentheses. Thus, applicants believe this rejection has been overcome and applicants respectfully request its withdrawal.

E. The Office Action states that claim 13 is allegedly indefinite in the recitation of "IgG-like molecule" because it is not clear what properties of the IgG molecule are intended to be within the metes and bounds of the claimed invention.

Applicants respectfully point out that molecules having structural characteristics of IgG are well recognized in the art and that the skilled artisan would readily identify such IgG-like molecules. Therefore, applicants believe that this term is sufficiently definite and respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending claims in this application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No fees are believed due. However, the Examiner is authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: BOX AF, Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Mary L. Miller — January 7, 2002
Date

Marked up version of claim amendments responsive to May 4, 2001 Office Action

U.S. Serial No. 09/091,578

13. (Thrice amended) The protein of claim [3] 67, wherein the target is a biological entity.

14. (Thrice amended) The protein of claim [3] 67, wherein the target is an organ, tumor, tissue, cell, virus, or microorganism.

15. (Thrice amended) The protein of claim [3] 67, wherein the target is a synthetic or naturally occurring macromolecule.

16. (Thrice amended) The protein of claim [3] 67, wherein the target is a protein.

17. (Thrice amended) The protein of claim [3] 67, wherein the target is a cell surface protein.

18. (Thrice amended) The protein of claim [3] 67, wherein the target is an integrin.

19. (Thrice amended) The protein of claim [3] 67, wherein the target is an integrin that binds to an Arg-Gly-Asp [(RGD)] tripeptide motif.

20. (Thrice amended) The protein of claim [3] 67, wherein the target is αIIbβ3 integrin.

21. (Thrice amended) The protein of claim [3] 67, wherein the target is $\alpha v\beta_3$ integrin.

22. (Thrice amended) The protein of claim [3] 67, wherein the optimized, protein surface loop is a complementarity determining region of an IgG-like molecule.

23. (Thrice amended) The protein of claim [3] 67, wherein the optimized, surface loop is a complementarity determining region of an antibody molecule.

24. (Twice amended) The [targeted agent or] protein of claim 23, wherein the complementarity determining region is heavy chain complementarity determining region 3 [(HCDR3)] of monoclonal antibody Fab-9.

65. (Amended) The protein of claim [3] 67, wherein the protein is loop-grafted tissue type plasminogen activator [(LG-tPA)].